Claims 1, 3-15, 17-42, 47-49, 51-57, 59-66 and 67-76 are pending. Claims 67-76 have been withdrawn as directed to a non-elected invention. Claims 1, 3, 5-6, 15, 19, 21, 25, 26, 35, 41, 42, 47, 49, 52, 59, 63, and 77 have been amended hereinabove. Claims 4, 48, and 66 have been canceled. Accordingly, claims 1, 3, 5-15, 17-42, 47, 49, 51-57, 59-65, and 77 are presently being examined.

Changes to the specification involve merely a typographical error. Applicants incorrectly indicated that Yokochi et al., J. Immunol. 128:823 was published in 1981 when in fact the reference was published in 1982 (see Information Disclosure Statement, Exhibit CD).

Support for amended claims 1, 3, 5-6, 15, 19, 21, 25, 26, 35, 41, 42, 47, 49, 52, 59, 63, and 77 may be found as follows.

Support for amended claim 1 may be found in the specification as originally filed at page 6, lines 34-35.

Support for amended claim 3 may be found in the specification as originally filed at page 7, line 22.

Support for amended claim 5 may be found in the specification as originally filed at page 7, lines 28-35.

Support for amended claim 6 may be found in the specification as originally filed at page 7.

Support for amended claim 15 may be found in the specification as originally filed at page 7, lines 15-16.

Support for amended claim 19 may be found in the specification as originally filed at page 19, lines 34-35.

Support for amended claim 21 may be found in the specification

as originally filed at page 19, lines 34-35.

Support for amended claim 25 may be found in the specification as originally filed at page 7, lines 28-35.

Support for amended claim 26 may be found in the specification as originally filed at page 19, lines 34-35.

Support for amended claim 35 may be found in the specification as originally filed at page 23, lines 1-11.

Support for amended claim 41 may be found in the specification as originally filed at page 7, line 22.

Support for amended claim 42 may be found in the specification as originally filed at page 7, lines 28-35.

Support for amended claim 47 may be found in the specification as originally filed at page 7, lines 28-35.

Support for amended claim 49 may be found in the specification as originally filed at page 13, lines 7-11.

Support for amended claim 52 may be found in originally filed claim 52.

Support for amended claim 59 may be found in originally filed claim 59.

Support for amended claim 63 may be found in the specification as originally filed at page 6, lines 34-35.

Support for amended claim 77 may be found in the specification as originally filed at page 7, lines 22.

Applicants maintain that the amendments to the claims do not

raise an issue of new matter. Support for the amendment to the claims may be found in the specification and claims as originally filed as indicated hereinabove.

In view of the preceding amendments and the remarks which follow, applicants respectfully request that the Patent Office enter the amendments to the claims.

Moreover, in view of the changes hereinabove and the following comments, applicants respectfully request that the Patent Office reconsider and withdraw the various grounds for objection and rejection set forth in the December 4, 1992 Office Action.

PARAGRAPH 21 OF THE OFFICE ACTION

The Patent Office objected to the specification under 35 U.S.C. § 112, first paragraph, as allegedly failing to provide an adequate written description of the invention and failing to adequately teach how to make and/or use the invention, i.e., failing to provide an enabling disclosure.

Specifically in subparagraph (a), the Patent Office has taken the position that the disclosure has not enabled a person of ordinary skill in the art to use the claimed methods in their broadest application, i.e., for in vivo use in humans.

In response, applicants respectfully traverse the Patent Office's objection for the reasons which follow.

Applicants have taught how to use the claimed invention. In fact, applicants have stated that "it is expected that administration of the B7 antigen will result in an effect similar to the use of anti-CD28 monoclonal antibodies (mAbs) reactive with the CD28 receptor in vivo" (specification page 21, first full paragraph).

Further, it is not necessary to specify the dosage or method of use if it is obvious to one skilled in the art that such information could be obtained without undue experimentation. MPEP §608.1(p) at page 600-43.

Moreover, applicants have provided in the specification, as originally filed, statements of utility which contain within it connotations of how to use. Therefore, 35 U.S.C. § 112 is satisfied. (MPEP § 608.01(p) at page 600-43, left column, first full paragraph).

In light of the discussion hereinabove, applicants respectfully request that the Patent Office reconsider and withdraw the objection to the specification under 35 U.S.C. § 112, first paragraph.

PARAGRAPH 23 OF THE OFFICE ACTION

The Patent Office also rejected claims 1, 3-10, 13-15, 17-24, 26-32, 35-42, 47-49, 51-57, 59-66, and 77 under 35 U.S.C. § 112 first paragraph, as the disclosure is allegedly enabling only for claims limited to in vitro regulation of T cell responses.

Based upon the foregoing reasons set forth in paragraph 21 hereinabove for objecting to the specification, applicants request that the Patent Office reconsider and withdraw the rejection of claims 1, 3-10, 13-15, 17-24, 26-32, 35-42, 47-49, 51-57, 59-66, and 77 under 35 U.S.C. § 112, first paragraph.

PARAGRAPH 26 OF THE OFFICE ACTION

At page 4 of the Office Action, the Patent Office indicated that the applicants are under an obligation to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Patent Office to consider the applicability of potential 35 U.S.C. §

102(f) or § 102(g) prior art under 35 U.S.C. § 103.

In response, applicants confirm that all claims were commonly owned at the time of the invention.

PARAGRAPH 27 OF THE OFFICE ACTION

The Patent Office provisionally rejected claims 1, 3-15, 17-42, 47-49, 51-57, 59-66, and 77 under 35 U.S.C. § 103 as allegedly obvious over a co-pending application, namely U. S. Serial No. 547,980.

In response, applicants contend that U. S. Serial No. 547,980 has now been abandoned. In support of this statement, applicants provide a copy of the Notice of Abandonment in connection with this application (annexed hereto as Exhibit 1).

PARAGRAPH 28 OF THE OFFICE ACTION

The Patent Office also provisionally rejected claims 1, 3-15, 17-42, 47-49, 51-57, 59-66, and 77 under the judicially created doctrine of obviousness type double patenting as allegedly unpatentable over claims 1-29 of co-pending application, namely, U.S. Serial No. 547,980.

In response, applicants once again point out that U. S. Serial No. 547,980 has been abandoned. In support of this statement, applicants provide a copy of the Notice of Abandonment issued in connection with U. S. Serial No. 547,980 (annexed hereto as Exhibit 1). Thus, this basis for rejection is mooted.

PARAGRAPH 30 OF THE OFFICE ACTION

At page 5 of the Office Action, the Patent Office objected to the specification under 35 U.S.C. § 112, first paragraph as allegedly failing to provide an adequate written description of the

invention and failing to adequately teach how to make and/or use the invention. Specifically, the Patent Office has taken the position that the specification attempts to incorporate essential material by reference to a journal. Therefore, the Patent Office has suggested that applicants incorporate this material into the specification.

In response, applicants respectfully contend that in the specification of the subject application, applicants refer to publications, such as the Rosenberg reference, which describes well known procedures commonly utilized in the art to which the subject application pertains. These references are well known and is frequently cited as standard molecular biological procedures. The references cited are merely examples of various procedures to obtain the desired result. A person of skill in the art would be well versed in the procedures described in the cited references. Applicants maintain that the cited references are not essential to support the claims, nor are they essential for adequate disclosure of the invention. Clearly, it is well established in the law that a specification need not disclose and preferably omits that which is well known in the art. Spectra Physics, Inc. v. Coherent Inc., 3 U.S.P.Q. 2d 1737 (Fed. Cir. 1987).

Applicants contend that the references cited in the specification of the subject application are nonessential subject matter and their inclusion is proper for purposes of illustrating the state of the art.

Accordingly, applicants respectfully request that the Patent Office reconsider and withdraw the objection to the incorporation by reference in the specification of the subject application.

PARAGRAPH 32 OF THE OFFICE ACTION

The Patent Office rejected claims 19-24, 26-32, and 63-66 under

35 U.S.C. § 112, first paragraph as the disclosure is allegedly enabling only for claims limited to CD28 positive T cells.

In response, applicants have amended claims 19, 26 and 63 in accordance with the Patent Office's suggestion. Accordingly, the rejection of these claims and the claims which depend thereon, i.e., claims 20-24, 27-32, and 64-66, have been rendered moot.

PARAGRAPH 33 OF THE OFFICE ACTION

The Patent Office rejected claims 3-8, 41, 42, and 47-49 under 35 U.S.C. § 112, first paragraph as the disclosure is allegedly enabling only for claims limited to a B7 fragment or a derivative which represents (1) an amino acid sequence containing residues from about position 1 to about position 215 of B7 corresponding to the extracellular domain of the B7 antigen; and (2) a fusion protein as set forth in step (1) hereinabove and a second amino acid sequence corresponding to the hinge, CH2 and CH3 regions of human IgC-gamma-1.

In response, applicants have amended claims 3, 41, 42, and 47 in accordance with the Patent Office's suggestion. Accordingly, the rejection of these claims have been rendered moot. Further, the rejection to claims 4-8 and 48-49 which depend on claims 3, 41, and 42 directly or indirectly has also been overcome.

PARAGRAPH 34 OF THE OFFICE ACTION

The Patent Office also rejected claims 9, 10, 56 and 57 under 35 U.S.C. § 112, first paragraph as the disclosure is allegedly enabling only for claims limited to immobilized B7 antigen on CHO cells.

Applicants respectfully traverse the Patent Office's position. In fact, appropriate cells include mammalian cells such as COS, CHO, VERO, and HeLa cells (specification at page 15, lines 33-

34). Also, although preferred host cells for expression of the DNA constructs include eukaryotic cells such as COS or CHO cells, eukaryotic microbes may be used as hosts (specification at page 16, lines 20-23). For example, laboratory strains of Saccharomyces cerevisiae, Baker's yeast, are most used although other strains such as Schizosaccharomyces pombe may be used (specification at page 16, lines 23-24).

PARAGRAPH 35 OF THE OFFICE ACTION

On page 6 of the Office Action, the Patent Office rejected claims 13 and 14 under 35 U.S.C. § 112, first paragraph as the disclosure is allegedly enabling only for claims limited to in vitro use without the addition of a lymphokine. Allegedly, applicants' disclosure does not enable the use of the method in vivo or the use of the method in conjunction with a lymphokine.

In response, applicants respectfully traverse the Patent Office's rejection of claims 13-14 for the reasons which follow.

Contrary to the Patent Office's position, applicants' disclosure does enable the use of the claimed methods.

In fact, applicants provide the following:

> "administration of B7 antigen, e.g. as a soluble B7Ig fusion protein to react with CD28 positive T cells, will bind the CD28 receptor on the T cells and result in inhibition of the functional responses of T cells. Under conditions where T cell interactions are occurring as a result of contact between T cells and B cells, binding of introduced B7 antigen in the form of a fusion protein that binds to CD28 receptor on CD28 positive T cells should interfere, i.e. inhibit, the T cell interactions with B cells. Likewise, administration of the CD28 antigen, or its fragments and derivatives in vivo, for example in the form of a soluble CD28Ig fusion protein, will result in binding of the soluble CD28Ig to B7 antigen, preventing the endogenous stimulation of CD28 receptor by B7 positive cells such as activated B cells, and interfering with the interaction of B7 positive cells with T cells" (specification at page 21, lines 17-32).

Applicants contend that it would be well within one having ordinary skill in the art to know that the claimed proteins may be administered to a host subject in a variety of routes including injection intratumorally, intravenously, intraarterially, subcutaneously, or intramuscularly.

Additionally, applicants respectfully contend that the dosage of the B7Ig fusion protein would vary with various factors such as the type of subject (e.g., its height and weight) the purpose of the treatment, the mode of administration, and the determination of such factors would be well within the skill of one skilled in the art. The interrelationship of dosages for animals of various sizes and species and humans based on mg/m^2 of surface area is described by Freireich, E.J., et al. Quantitative Comparison of Toxicity of Anticancer Agents in Mouse, Rat, Hamster, Dog, Monkey and Man. Cancer Chemother, Rep., 50, No.4, 219-244, May 1966 (annexed hereto as Exhibit 2).

Adjustments in the dosage regimen may be made to optimize the growth inhibiting response. Doses may be divided and administered on a daily basis or the dose may be reduced proportionally depending upon the situation. For example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the specific therapeutic situation.

Further, contrary to the Patent Office's position, applicants respectfully contend that <u>in vitro</u> data herein correlates with <u>in vivo</u> results (specification at page 21, lines 1-9 and page 24, lines 6-12). Figures 1-4 of D. Lenschow et al. ((1992) Science <u>257</u>:789-792 entitled "Long Term Survival of Xenogeneic Pancreatic Islet Grafts Induced by CTLA4Ig" already of record) include <u>in vivo</u> data in mouse showing that blocking the CD28 receptor from binding the B7 antigen results in manipulating the mouse immune system into accepting transplanted tissue instead of attacking it and thereby preventing the rejection of transplanted tissue.

Further, applicants respectfully contend that since applicants have taught how to make and use the claimed method, the use of a lymphokine or cytokine would be well within the skill in the art and thus is also enabled by the specification (specification at page 1, line 7; page 26, lines 1-18; page 44, lines 1-13).

PARAGRAPH 36 OF THE OFFICE ACTION

The Patent Office rejected claim 15 under 35 U.S.C. § 112, first paragraph, as the disclosure is allegedly enabling only for claims limited to use of the method in conjunction with anti-CD2. Allegedly, applicants' disclosure does not enable the use of the method with anti-CD3.

In response, applicants respectfully point out that applicants have taught that the method for reacting a ligand for CD28 with T cells may additionally include the use of anti-CD monoclonal antibodies such as anti-CD2 and/or anti-CD3 monoclonal antibody (specification at page 7 and page 25, lines 16-18).

Accordingly, applicants respectfully request that the Patent Office reconsider and withdraw the rejection.

PARAGRAPH 37 OF THE OFFICE ACTION

The Patent Office also rejected claims 35-40 under 35 U.S.C. § 112, first paragraph, as the disclosure is allegedly enabling only for claims limited to the monoclonal antibody 9.3. The Patent Office has taken the position that the disclosure does not enable all possible antibodies directed to CD28.

Applicants respectfully disagree with the Patent Office's position for the reasons which follow.

The methods for preparing monoclonal antibodies directed against

CD28 are well established in the monoclonal antibody art. Further, it is not necessary to specify the method of use if it is obvious to one skilled in the art that such information could be obtained without undue experimentation. MPEP §608.1(p) at page 600-43.

In view of the aforementioned discussion, applicants respectfully request that the Patent Office reconsider and withdraw the rejection.

PARAGRAPH 38 OF THE OFFICE ACTION

The Patent Office further rejected claims 47-49, 51-57 and 77 under 35 U.S.C. § 112, first paragraph, as the disclosure is allegedly enabling only for claims limited to a CD28 receptor ligand that is B7Ig or monoclonal antibody 9.3. The Patent Office has taken the position that the specification does not provide an enabling disclosure for all possible receptor ligands.

In accordance with the Patent Office's statement, applicants have amended the claims to include that the ligand comprises a portion of the extracellular domain of the B7 antigen.

Keep in mind that the B7 antigen in the form of B7Ig fusion protein, or in combination with immunosuppressants such as cyclosporine, may be used for blocking T cell proliferation in GVH disease (specification at page 26, lines 32-35). In addition, B7Ig fusion protein may be used to crosslink the CD28 receptor, for example by contacting T cells with immobilized B7Ig fusion protein, to assist in recovery of immune function after bone marrow transplantation by stimulating T cell proliferation (specification at page 27, lines 1-4).

Accordingly, applicants respectfully request that the Patent Office reconsider and withdraw the rejection.

PARAGRAPH 39 OF THE OFFICE ACTION

The Patent Office rejected claims 1, 3-10, 13-15, 17-24, 26-32, 35-42, 47-49, 51-57, 59-66 and 77 under 35 U.S.C. § 112, first paragraph, as the disclosure is allegedly enabling only for claims limited to inhibiting the interaction of CD28 positive cells with B7 positive cells in vitro. The Patent Office has taken the position that the claims are clearly outside of the enabling disclosure as allegedly responsible for regulating all functional T cell responses, including production of cytokines, note specifically page 25, lines 25-35.

In response applicants have amended such claims as including only CD28 positive T cells.

Accordingly, applicants respectfully request that the Patent Office reconsider and withdraw the rejection.

PARAGRAPH 40 OF THE OFFICE ACTION

The Patent Office rejected claims 52-57 and 59-62 under 35 U.S.C. § 112, first paragraph, as the disclosure is allegedly enabling only for claims limited to immune system diseases which are caused by the interaction of B7 with CD28 positive cells and cancers specifically responsive to inhibiting the B7/CD28 interaction. The Patent Office has taken the position that the disclosure does not enable the claims as drawn to a treatment for all immune system diseases or the treatment for all cancers.

In response, applicants have amended such claims to include diseases associated with the interaction of B7 with CD28 positive cells and cancers responsive to B7/CD28 interaction.

Accordingly, applicants respectfully request that the Patent Office reconsider and withdraw the rejection.

PARAGRAPH 41 OF THE OFFICE ACTION

The Patent Office rejected claim 66 under 35 U.S.C. § 112, first paragraph, as the disclosure is allegedly enabling only for claims limited to inhibiting the interaction of B7 with CD28 positive cells. The Patent Office has taken the position that the use of the method as an immunosuppressant in conjunction with cyclosporine has not been enabled in the instant specification.

In response, applicants have canceled claim 66. Accordingly, applicants respectfully contend that the rejection has been rendered moot.

PARAGRAPH 42 OF THE OFFICE ACTION

The Patent Office rejected claim 17 under 35 U.S.C. § 112, first paragraph, as the disclosure is allegedly enabling only for claims limited to reacting CHO cells expressing B7 or fusion proteins with T-cells. The Patent Office has taken the position that the disclosure does not support the claims of reacting B-cells with T-cells.

Applicants respectfully disagree with the Patent Office's position for the reasons which follow.

The present invention relates to the identification of an interaction between the CD28 receptor and its ligand, the B7 antigen, and to a method for regulating cellular interactions using the antigen, fragments and derivatives thereof (specification at page 1). The specification provides that the B7 antigen, or its fragments or derivatives are reacted with CD28 positive T cells to regulate T cell interactions with other cells (specification at pages 6-7 and generally throughout the application).

In view of this discussion, applicants respectfully request that

the Patent Office reconsider and withdraw the rejection to the claims.

PARAGRAPH 43 OF THE OFFICE ACTION

The Patent Office also rejected claims 19-22 and 59-62 under 35 U.S.C. § 112, first paragraph, as the disclosure is allegedly enabling only for claims limited to a B7 antigen reactive ligand which is either:

A) monoclonal antibody BB-1 or a $F(ab)_2$ fragment of said antibody, or

B) the CD28Ig fusion protein.

Allegedly, the specification does not enable every possible ligand for the B7 antigen.

Applicants respectfully disagree with the Patent Office's position for the reasons which follow.

The claimed invention is directed to a method of regulating functional T cell responses of CD28 positive T cells comprising reacting B7 positive cells with any ligand reactive with B7 antigen. Applicants have shown that CD28 receptor will bind the B7 antigen (specification at page 8 and generally throughout the specification). However, it is generally known that other receptors such as CTLA-4 will also bind the B7 antigen. The invention is not in binding the B7 antigen but the realization that functional T cells responses of CD28 positive T cells may be regulated by binding the B7 antigen. This realization is important since before applicants' invention no one knew that by binding the B7 antigen one can in turn regulate functional T cell responses.

Applicants respectfully contend that the CD28 receptor exemplifies one type of ligand but it is generally known in the art that many ligands bind B7. Clearly, case law provides that applicants need not teach what is already well known in the art

(In re Wands, 8 U.S.P.Q.2d 1400, 1404).

In view of this discussion, applicants respectfully request that the Patent Office reconsider and withdraw this rejection.

PARAGRAPH 44 OF THE OFFICE ACTION

The Patent Office also rejected claims 18 and 64 under 35 U.S.C. § 112, first paragraph, as the disclosure is allegedly enabling only for claims limited to the B7Ig fusion protein.

The Patent Office has taken the position that the specification does not enable every possible soluble form of the B7 antigen.

Applicants respectfully disagree with the Patent Office's position. Applicants have taught methods for expressing soluble forms of the B7 antigen as follows:

> "expression of soluble forms of CD28 and B7, constructs were made (OMCD28 and OMB7) in which stop codons were introduced upstream of the transmembrane domains and the native signal peptides were replaced with the signal peptide from oncostatin M (Malik et al., Mol. Cell Biol. 9:2847 (1989)). These were made using synthetic oligonucleotides for reconstruction (OMCD28) or as primers (OMB7) for PCR. OMCD28, is a CD28 cDNA modified for more efficient expression by replacing the signal peptide with the analogous region from oncostatin M. CD28Ig and B7Ig fusion constructs were made in two parts. The 5' portions were made using OMCD28 and OMB7 as templates and the oligonucleotide, CTAGCCACTGAAGCTTCACCATGGGTGTACTGCTCACAC (SEQ ID NO:1) (corresponding to the oncostatin M signal peptide) as a forward primer, and either TGGCATGGGCTCCTGATCAGGCTTAGAAGGTCCGGGAAA (SEQ ID NO:2), or, TTTGGGCTCCTGATCAGGAAAATGCTCTTGCTTGGTTGT (SEQ ID NO:3) as reverse primers, respectively. Products of the PCR reactions were cleaved with restriction endonucleases (Hind III and BclI) as sites introduced in the PCR primers and gel purified.
>
> The 3' portion of the fusion constructs corresponding to human Ig Cγ1 sequences was made by a coupled reverse transcriptase (from Avian myeloblastosis virus; Life Sciences Associates, Bayport, NY)-PCR reaction using RNA from a myeloma cell line producing human-mouse chimeric mAb L6 (provided by Dr. P. Fell and M. Gayle, Bristol-Myers

Squibb Pharmaceutical Research Institute, Seattle, WA) as template. The oligonucleotide, AAGCAAGAGCATTTTCCTGATCA GGAGCCCAAATCTTCTGACAAAACTCACACATCCCCACCGTCCCCAGCACCTGAACT CCTG (SEQ ID NO:4), was used as forward primer, and CTTCGACCAGTCTAGAAGCATCCTCGTGCGACCGCGAGAGC (SEQ ID NO:5) as reverse primer. Reaction products were cleaved with BclI and XbaI and gel purified. Final constructs were assembled by ligating HindIII/BclI cleaved fragments containing CD28 or B7 sequences together with BclI/XbaI cleaved fragment containing Ig Cγ1 sequences into HindIII/XbaI cleaved CDM8. Ligation products were transformed into MC1061/p3 E. coli cells and colonies were screened for the appropriate plasmids. Sequences of the resulting constructs were confirmed by DNA sequencing. The DNA used in the B7 construct encodes amino acids from about position 1 to about position 215 of the sequence corresponding to the extracellular domain of the B7 antigen, and for CD28, the DNA encoding amino acids from about position 1 to about position 134 of the sequence corresponding to the extracellular domain of the CD28 receptor.

CD5Ig was constructed in identical fashion, using CATTGCACAGTCAAGCTTCCATGCCCATGGGTTCTCTGGCCACCTTG (SEQ ID NO:6), as forward primer and ATCCACAGTGCAGTGATCATTTGGATCCTGGCATGTGAC (SEQ ID NO:7) as reverse primer. The PCR product was restriction endonuclease digested and ligated with the Ig Cγ1 fragment as described above. The resulting construct (CD5Ig) encodes an amino acid sequence containing residues from about position 1 to about position 347 of CD5, two amino acids introduced by the construction procedure (amino acids DQ), followed by the Ig Cγ1 hinge region (specification at page 53).

Further, applicants taught how to make soluble derivatives of B7 as follows:

"cDNA constructs were made encoding molecules truncated at the NH_2-terminal side of their transmembrane domains. In both cases, the native signal peptides were replaced with the signal peptide from oncostatin M (Malik, supra, 1989), which mediates efficient release of secreted proteins in transient expression assays. The cDNAs were cloned into an expression vector, transfected into COS cells, and spent culture medium was tested for secreted forms of B7 and CD28. In this fashion, several soluble forms of B7 were produced, but in repeated attempts, soluble CD28 molecules were not detected.

The next step was to construct receptor Ig Cγ1 fusion proteins. The DNAs encoding amino acid sequences corresponding to B7 and CD28 extracellular regions, preceded by the signal peptide to oncostatin M, were fused in frame to an Ig Cγ1 cDNA, as shown in Figure 9. During

> construction, the Ig hinge disulfides were mutated to serine residues to abolish intrachain disulfide bonding. The resulting fusion proteins were produced in COS cells and purified by affinity chromatography on immobilized protein A as described below. Yields of purified protein were typically 1.5-4.5 mg/liter of spent culture medium" (specification at page 54-55).

By providing methods to make soluble forms of the B7 antigen, applicants have taught the claimed invention including the use of soluble B7 antigen. Thus, the practice of the claimed invention does not involve undue experimentation.

In view of this discussion, applicants respectfully request that the Patent Office reconsider and withdraw the rejection.

PARAGRAPH 45 OF THE OFFICE ACTION

The Patent Office rejected claim 25 under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to monoclonal antibody BB-1. Allegedly, the specification does not enable every possible antibody to the B7 antigen.

Applicants respectfully traverse the Patent Office's position for the reasons which follow.

The claimed monoclonal antibody is not directed to every possible antibody to the B7 antigen. In fact, claim 25 is directed to a monoclonal antibody reactive with a B7Ig fusion protein. Applicants respectfully contend that it would be well within the skill of one in the art to produce the claimed monoclonal antibody since applicants have deposited the amino acid sequence for the B7Ig encoded by DNA having ATCC No. 68627.

In view of this discussion, applicants respectfully request that the Patent Office reconsider and withdraw the rejection.

PARAGRAPH 46 OF THE OFFICE ACTION

The Patent Office rejected claims 26-32 under 35 U.S.C. § 112, first paragraph, as the disclosure is allegedly enabling only for claims limited to the CD28Ig fusion protein containing amino acid residues from about position 1 to 134 and a second amino acid sequence corresponding to the hinge CH2 and CH3 regions of human Ig C-gamma-1.

Applicants respectfully disagree.

The invention provides a method for regulating immune responses by contacting CD28 positive T cells with fragments containing at least a portion of the DNA sequence encoding the amino acid sequence corresponding to the extracellular domain of B7 antigen (specification at page 7).

Additionally, the invention provides in a preferred embodiment, DNA encoding amino acid residues from about position 1 to about position 215 of the sequence corresponding to the extracellular domain of B7 antigen joined to DNA encoding amino acid residues of the sequences corresponding to the hinge, CH2 and CH3 regions of human Ig Cγ1 to form a DNA fusion product which encodes B7Ig fusion protein (specification at page 7).

Further, the invention provides in another preferred embodiment, DNA encoding amino acid residues from about position 1 to about position 134 of the sequence corresponding to the extracellular domain of the CD28 receptor is joined to DNA encoding amino acid residues of the sequences corresponding to the hinge, CH2 and CH3 regions of human Ig Cγ1 to form a CD28Ig fusion protein (specification at pages 7-8).

The disclosure is not merely enabling for only claims limited to the CD28Ig fusion protein containing amino acid residues from

about position 1 to 134 and a second amino acid sequence corresponding to the hinge CH2 and CH3 regions of human Ig C-gamma-1 and thus applicants respectfully request that the Patent Office reconsider and withdraw the rejection of the claims.

PARAGRAPH 47 OF THE OFFICE ACTION

The Patent Office rejected claims 11 and 12 under 35 U.S.C. § 103 as being unpatentable over Freeman et al. (CA) in view of Capon et al. (CE).

Claims 11 and 12 are drawn to a B7 fusion protein with the human immunoglobulin C-gamma-1.

The Patent Office stated that Freeman et al. teach the complete sequence of the B7 antigen (figure 3A). Further, Freeman et al. allegedly do not teach a fusion protein of the B7 antigen to the human immunoglobulin C-gamma-1.

The Patent Office also stated that Capon et al. teaches fusing human immunoglobulin C-gamma-1 to CD4 in order to prolong serum half life.

The Patent Office has taken the position that it would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to apply the teachings of Capon et al. to those of Freeman et al. to obtain a fusion of B7 with the human immunoglobulin C-gamma-1 in order to obtain a soluble B7 protein with a long serum half life, see entire Capon et al. document.

Applicants respectfully disagree with the Patent Office's position for the reasons which follow.

A. THE COMBINATION OF FREEMAN AND CAPON DOES NOT RENDER OBVIOUS THE CLAIMED INVENTION

Freeman teaches the nucleotide sequence of the B7 cDNA clone and predicted amino acid sequence and hydrophobicity of the B7 polypeptide (Freeman at page 2717). However, Freeman does not teach that the B7 antigen could be expressed.

Capon teaches methods for producing an antibody-like molecule containing the gp120 binding domain of the receptor for HIV. However, Capon does not teach that the methods therein can be used for producing B7Ig.

Applicants respectfully contend that in order to produce the claimed invention the correct multiple joining segments are attached to the constant segments. The linkage of a variable segment to a constant segment may occur next to any of the joining segments and depending on which joining segment is used, a different group of amino acids will be found inserted between the amino acids encoded by the variable segment and those encoded by the constant segment (Recombinant DNA: A Short Course edited by James D. Watson et al. (1983) at pages 117-126 annexed herewith as Exhibit 3).

The joining segment is not B7. Therefore, one skilled in the art must make sure that any non-B7 segment in the antibody does not interfere with the tertiary structure characteristics of the Ig superfamily.

Before applicants' invention no one had ever expressed the B7 antigen because it was difficult to do. The expression of the B7 antigen was not routine. In fact, during construction, the Ig hinge disulfides of B7Ig were mutated to serine residues to abolish intrachain disulfide bonding (specification at page 55). This mutation permitted expression of the B7 antigen

(specification at page 55).

Moreover, the rejections under 35 U.S.C. §103 do not make out a prima facie case of obviousness. There is no teaching or suggestion in the cited references that a fusion molecule of B7Ig could be prepared and that such a molecule would retain activity.

In view of the aforementioned discussion, applicants respectfully request that the Patent Office reconsider and withdraw the rejection to the claims.

PARAGRAPH 48 OF THE OFFICE ACTION

The Patent Office rejected claim 25 under 35 U.S.C. § 103 as allegedly unpatentable over Yokochi et al. (CD). Claim 25 is drawn to a monoclonal antibody reactive with the B7 fusion protein. The Patent Office stated that Yokochi et al. produced monoclonal antibody BB-1.

Applicants respectfully disagree with the Patent Office's position.

Yokochi teaches that COS cells transfected with a cDNA clone encoding a B cell activation antigen have been shown to stain by labeled mAb BB-1 (specification at page 6, lines 1-12).

However, Yokochi does not teach that mAb BB-1 would recognize the claimed monoclonal antibody which is reactive with the B7 fusion protein. The B7 fusion protein has a sequence different from B7 antigen.

Because mAb BB-1 recognizes B7 antigen does not means that it will recognize a protein having the extracellular domain of the B7 antigen and Ig sequences. In fact, Yokochi's antibody cannot recognize and bind to both portions of B7 and Ig sequences because it binds only to B7. Thus, Yokochi does not suggest the

claimed monoclonal antibody.

In view of the discussion hereinabove, applicants respectfully request that the Patent Office reconsider and withdraw the rejection.

PARAGRAPH 49 OF THE OFFICE ACTION

The Patent Office rejected claims 33 and 34 under 35 U.S.C. § 103 as being unpatentable over Aruffo et al. (AV) in view of Capon et al. (CE).

Claims 33 and 34 are drawn to a CD28 fusion protein with the human immunoglobulin C-gamma-1.

The Patent Office stated that Aruffo et al. teach the complete sequence of the CD28 molecule (figure 2). Further, the Patent Office stated that Aruffo et al. do not teach a fusion protein of the B7 antigen to the human immunoglobulin C-gamma-1.

The Patent Office additionally stated that Capon et al. teaches fusing human immunoglobulin C-gamma-1 to CD4 in order to prolong serum half life.

The Patent Office has taken the position that it would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to apply the teachings of Capon et al. to those of Aruffo et al. so as to obtain a fusion of CD28 with the human immunoglobulin C-gamma-1 in order to obtain a soluble CD28 protein with a long serum half life.

Applicants respectfully disagree with the Patent Office's position.

A. THE COMBINATION OF ARUFFO AND CAPON DOES NOT RENDER OBVIOUS THE CLAIMED INVENTION

Aruffo teaches the nucleotide sequence of the CD28 cDNA (Aruffo at page 8574). However, the in vivo function of CD28 antigen is not known (specification at page 2).

Moreover, before applicants invention, no one had expressed the CD28 antigen. In fact, the expression of the CD28 Ig is not routine. In order to overcome the problems, the DNAs encoding amino acid sequences corresponding to CD28 extracellular regions, preceded by the signal peptide to oncostatin M, were fused in frame to an Ig Cγ1 cDNA, as shown in Figure 9 (specification at page 55). During construction, the Ig hinge disulfides were mutated to serine residues to abolish intrachain disulfide bonding (specification at page 55). Then the resulting fusion proteins were produced in COS cells and purified by affinity chromatography on immobilized protein A as described in the specification.

Moreover, because CD28 receptors occur in nature as dimers, it is believed that successful expression of these proteins requires an expression system which permits these proteins to form as dimers (specification at page 17, lines 33-35). Truncated versions of these proteins (i.e. formed by introduction of a stop codon into the sequence at a position upstream of the transmembrane region of the protein) appear not to be expressed (specification at page 18, lines 1-5). The expression of CD28 antigen in the form of a fusion protein permits dimer formation of the protein (specification at page 18, lines 5-9). Thus, expression of CD28 antigen as a fusion product is preferred in the present invention (specification at page 18, lines 5-9).

PARAGRAPH 50 OF THE OFFICE ACTION

Applicants are pleased that the Patent Office withdrew the rejection of claims 1-66 under 35 U.S.C. § 101.

PARAGRAPH 51 OF THE OFFICE ACTION

The Patent Office objected to the specification under 35 U.S.C. § 112, first paragraph, as allegedly failing to provide an adequate written description of the invention and failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure.

The Patent Office stated that applicants' arguments concerning the mouse studies which show in vivo efficacy of the claimed invention is unpersuasive. The Patent Office stated that animal models can only be used if they are accepted models for human therapy and the mouse appears not to be an accepted model for human therapy.

Further, the Patent Office has taken the position that there is nothing in the disclosure which supports in vivo use.

Applicants respectfully disagree with the Patent Office's position for the reasons which follow.

The use of the claimed invention for in vivo therapy is described as follows:

> "administration of B7 antigen, e.g. as a soluble B7Ig fusion protein to react with CD28 positive T cells, will bind the CD28 receptor on the T cells and result in inhibition of the functional responses of T cells. Under conditions where T cell interactions are occurring as a result of contact between T cells and B cells, binding of introduced B7 antigen in the form of a fusion protein that binds to CD28 receptor on CD28 positive T cells should interfere, i.e. inhibit, the T cell interactions with B cells. Likewise, administration of the CD28 antigen, or

its fragments and derivatives in vivo, for example in the form of a soluble CD28Ig fusion protein, will result in binding of the soluble CD28Ig to B7 antigen, preventing the endogenous stimulation of CD28 receptor by B7 positive cells such as activated B cells, and interfering with the interaction of B7 positive cells with T cells" (specification at page 20-21).

Applicants contend that determining the details involved in the in vivo use of the claimed invention would be well within the skill of one in the art. As stated previously administration of the B7 antigen or CD28 antigen would be well within one having ordinary skill in the art (specification at page 21, lines 17-32). Further, it would be well within one having ordinary skill in the art to know that the dosage of the B7Ig fusion protein would vary with various factors such as the type of subject (e.g., its height and weight) the purpose of the treatment, the mode of administration. Clearly, adjustments in the dosage regimen may be made to optimize the growth inhibiting response.

Applicants respectfully contend that dosage and administration of the B7 and CD28 antigens would depend on the subject and such determination would be well within one skilled in the art without undue experimentation.

As corroboration of the claimed invention and what is provided in the specification, Lenschow (i.e. Figures 1-4 of D. Lenschow et al. ((1992) Science 257:789-792 entitled "Long Term Survival of Xenogeneic Pancreatic Islet Grafts Induced by CTLA4Ig" already of record) shows that blocking the CD28 receptor from binding the B7 antigen results in manipulating in vivo the mouse immune system into accepting transplanted tissue instead of attacking it and thereby preventing the rejection of transplanted tissue (specification at pages 26-27).

It is not necessary to specify the dosage or method of use if it is obvious to one skilled in the art that such information could

be obtained without undue experimentation. MPEP §608.1(p) at page 600-43.

Accordingly, applicants respectfully request that the Patent Office reconsider and withdraw the objection to the specification.

PARAGRAPH 52 OF THE OFFICE ACTION

The Patent Office also rejected claims 1, 3-10, 13-15, 17-24, 26-32, 35-42, 47-49, 51-57 and 59-66 under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

For the reasons discusses at paragraph 51 hereinabove, applicants respectfully request that the Patent Office reconsider and withdraw the rejection to the claims.

PARAGRAPH 53 OF THE OFFICE ACTION

Applicants are pleased that the Patent Office withdrew the objection to the specification under 35 U.S.C. § 112, first paragraph.

PARAGRAPH 54 OF THE OFFICE ACTION

The Patent Office rejected claims 1, 3-10, 13-15, 17-24, 26-32, 35-42, 47-49, 51-57 and 59-66 under 35 U.S.C. § 112, first paragraph, as the disclosure is allegedly enabling only for claims limited to <u>in-vitro</u> regulation of T cell responses. See M.P.E.P. §§ 706.03(n) and 706.03(z). The Patent Office has taken the position that there is nothing in the disclosure which supports <u>in vivo</u> use. The Patent Office suggested that the claims be limited to <u>in vitro</u> use.

Applicants respectfully disagree with the Patent Office's

position for the following reasons.

Applicants contend that determining the details involved in the use of the claimed invention would be well within the skill of one in the art. It is not necessary to specify the dosage or method of use if it is obvious to one skilled in the art that such information could be obtained without undue experimentation. MPEP §608.1(p) at page 600-43.

For these reasons, applicants respectfully request that the Patent Office reconsider and withdraw the rejection to the claims.

PARAGRAPH 55 OF THE OFFICE ACTION

Applicants are pleased that the Patent Office withdrew the rejection of claims 15 and 21 under 35 U.S.C. § 112, second paragraph.

PARAGRAPH 56 OF THE OFFICE ACTION

Applicants are pleased that the Patent Office withdrew the rejection of claims 1, 15, 35-40, 51-52, 55, 56, 59, 60, 63, and 66 under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over Damle et al.

PARAGRAPH 57 OF THE OFFICE ACTION

The Patent Office provisionally rejected claims 1, 3-15, 17-42, 47-49, 51-57, 59-66 and 77 under 35 U.S.C. § 103 as allegedly obvious over co-pending application Serial No. 07/547980.

Applicants respectfully point out that the co-pending application has been abandoned. In support of this statement, applicants provide a copy of the Notice of Abandonment issued in connection with U.S. Serial No. 547,980 (annexed herewith as Exhibit 1).

In view of this discussion, applicants respectively request that the Patent Office reconsider and withdraw the rejection.

PARAGRAPH 58 OF THE OFFICE ACTION

The Patent Office provisionally rejected claims 1, 3-15, 17-42, 47-49, 51-57, 59-66 and 77 under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claim 1-29 of co-pending application Serial No. 07/547,980.

As stated previously, the co-pending application has been abandoned. In support of this statement, applicants provide a copy of the Notice of Abandonment issued in connection with U.S. Serial No. 547,980 (annexed herewith as Exhibit 1).

In view of this discussion, applicants respectively request that the Patent Office reconsider and withdraw the rejection.

PARAGRAPH 59 OF THE OFFICE ACTION

Applicants are pleased that the Patent Office withdrew the rejection of claims 1, 15, 35-40, 51-52, 55, 56, 59, 60, 63, and 66 under 35 U.S.C. § 103 as being unpatentable over Damle et al.

Because of the preceding discussion and amendments, applicants request that the Patent Office reconsider and withdraw the various grounds for objection and rejection set forth in the December 4, 1992 Office Action and earnestly solicit allowance of the claims now being examined.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone her at the number provided below.

No fee, other than the $110.00 extension fee, is deemed necessary

in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 19-2090.

Respectfully submitted,

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I hereby certify that this paper is being deposited this date with the U.S. Postal Service as first class mail addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231.

Signature 4/5/93 Date